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INITIAL SLOPE INDEX OF TOTAL CEREBRAL BLOOD FLOW MEASURED BY HYDROGEN CLEARANCE: A PRAGMATIC EVALUATION

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Research was conducted according to the principles enunciated in the "Guide for Laboratory Animal Facilities and Care," prepared by the National Academy of Sciences - National Research Council.

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FOREWORD
(Nontechnical summary)

A comparison is made between cerebral blood flows calculated from: (a) the slope of a best-fitting line of data from the first 2 min of the hydrogen washout curve, and (b) bicompartmental analysis of data from 10 min of washout curve. A linear regression analysis of 247 flows shows a high correlation coefficient, 0.9280. The initial slope index is not only easier to calculate but does not require that a long steady state be maintained during washout. The variability of the initial index method is no higher than that of the more tedious, but more theoretically correct, bicompartmental analysis.

ABSTRACT

An initial slope index of total cerebral blood flow, measured by hydrogen clearance from torcular blood, shows high correlation with flows calculated by bicompartmental analysis. In 247 flow measurements done on 41 rhesus monkeys, a linear regression analysis between these two methods of calculating flow shows a correlation coefficient of 0.9280 with a standard error about y values of ± 7.63. The initial slope index is not only faster to calculate but does not require that a steady state be maintained for 10 minutes.

I. INTRODUCTION

In 1970, Sveinsdottir et al.[5] made the comparison between regional cerebral blood flow values calculated by an initial slope index method and by the stochastic method of height-over-total-area and concluded that the 2-minute initial index method, although theoretically erroneous, contained essentially the same information as that obtained from the more laborious but more theoretically correct, stochastic method.

This report concerns the correlation between total cerebral blood flow values calculated by the initial slope index method and by bicompartmental analysis. An initial index of flow would be valuable in calculating total cerebral flow in that the assumption of a 10-minute steady state would not have to be made, and minor variations of base line would have only negligible effect.

II. METHODS

Our method of measuring total cerebral blood flow using hydrogen clearance and an electrode in the torcular Herophili has been described elsewhere.[3] Part of the skull at the inion was removed and a vascular electrode was passed through the dura into the torcular Herophili. In some animals multiple (5-8) electrodes were also passed stereotactically into the brain for simultaneously recording blood flow in tissue. All electrodes were anchored to the skull with methyl methacrylate. The reference electrode was a self-tapping stainless steel screw passed into the frontal bone. Hydrogen was added to the inspired gas mixture at the endotracheal tube entrance in a concentration that varied from 5 to 25 volumes percent, but was constant in each study. Hydrogen was usually given for 10 minutes, but in some experiments the period of inhalation was varied from 5 to 30 minutes. At the end of a predetermined

period, hydrogen flow was stopped abruptly and the recording of its clearance from torcular blood and tissue begun. The data used here were derived from 247 total cerebral blood flow studies done on 41 rhesus monkeys.

Flows were obtained during states of normocapnia, hypocapnia, and hypercapnia and ranged from 14 to 196 ml/100 g per min. It was determined earlier[3,4] that 40 seconds after hydrogen inhalation was stopped, arterial hydrogen concentration decreased to less than 10 percent of the original concentration; therefore, data from the first 40 seconds of the washout curve were not used.

III. THEORETICAL CONSIDERATIONS

The rate at which hydrogen is washed out of tissue is proportional to the blood flow through the tissue.[1] If the tissue being sampled is homogeneous, then the equation for the washout curve is monoexponential and blood flow can easily be calculated from the formula:

$$\bar{f} = \lambda \cdot k \tag{1}$$

where $\bar{f}$ is the flow in milliliters per gram per minute, λ is the blood:tissue partition coefficient, which for hydrogen is close to unity,[2] and k is the rate constant. The rate constant or slope can easily be obtained from the formula:

$$k = \frac{\ln C2 - \ln C1}{T2 - T1} \quad . \tag{2}$$

C1 and C2 are any values on the curve at times T1 and T2. Since the brain is not composed of homogeneously perfused tissue, the clearance curves are almost always biexponential and, therefore, are analyzed either stochastically (height-over-total-area) or bicompartmentally.[3] The latter was used for this report.

Bicompartmental analysis. For this method the data are graphed on semilogarithmic graph paper and the biexponential curve is, by standard curve stripping techniques, separated into the two component exponentials representing the fast and slow flow components, i.e., $y = Ae^{-k_1 t} + Be^{-k_2 t}$.

The average total flow, $\bar{f}$, is then calculated from the formula:[3]

$$\bar{f} = \frac{A + B}{\frac{A}{k_1} + \frac{B}{k_2}}$$

where $\bar{f}$ = average total blood flow, A = y intercept of the fast component, B = y intercept of the slow component, and k_1 and k_2 = rate constants (or slopes) of the fast and slow components, respectively.

Initial slope index. To use the initial slope index we assume that $k_1 = k_2 = k$, i.e., that the initial part of the washout curve can be fitted by a straight line. k is then calculated from formula (2) and $\bar{f}$ from formula (1). Data from the first 2 minutes of the clearance curve were used.

IV. RESULTS

A linear regression analysis of the two methods of calculating flow from the same data shows a high correlation coefficient, 0.9280 (Figure 1). Flows in the normal range,[3] centering about 52 ml/100 g per min, tended to be similar when calculated with either method. The 2-minute slope index tended to underestimate higher flows and overestimate lower flows, in comparison with flows calculated by bicompartmental analysis. The slope did not differ significantly from 1.0, but the difference between the intercept and zero was very highly significant ($p < 0.001$).

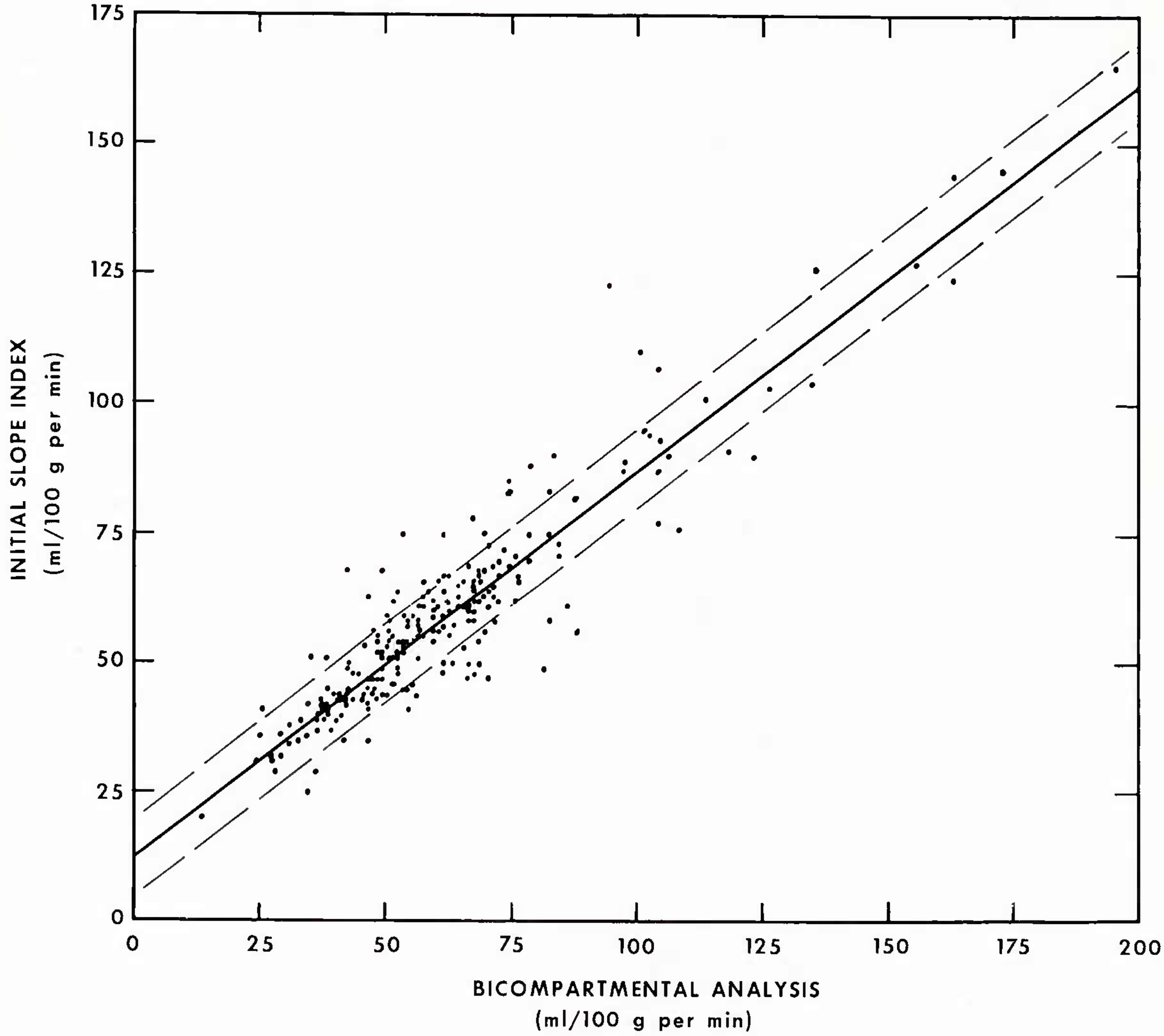

Figure 1. A linear regression analysis of flows calculated from the initial slope (ordinate) and by bicompartmental analysis (abscissa). n = 247, correlation coefficient 0.9280 $\pm$ 7.63 S.D. Equation for line: $y = 0.74x \pm 12.55$.

To determine whether flows calculated by either method differ in variability, data were selected from 12 experiments (61 flows) in which physiological parameters such as blood gases, blood pressure and temperature were kept stable for the duration of the experiment. In these instances flow values would be expected to remain constant. The variation coefficient ($\frac{\text{standard deviation}}{\text{mean value}} \times 100$) was calculated for each

experiment, for each method of calculating flow, and then averaged. The variation coefficient for the bicompartmental method was 13.9 which did not differ significantly from 13.0 for the initial slope index method. Also, there was no correlation between the magnitude of the flow values and the variability.

Linear regression analysis showed that the initial index of flow had a higher correlation to the slow component of flow, 0.7612 (Figure 2) than to the fast component, 0.6001 (Figure 3).

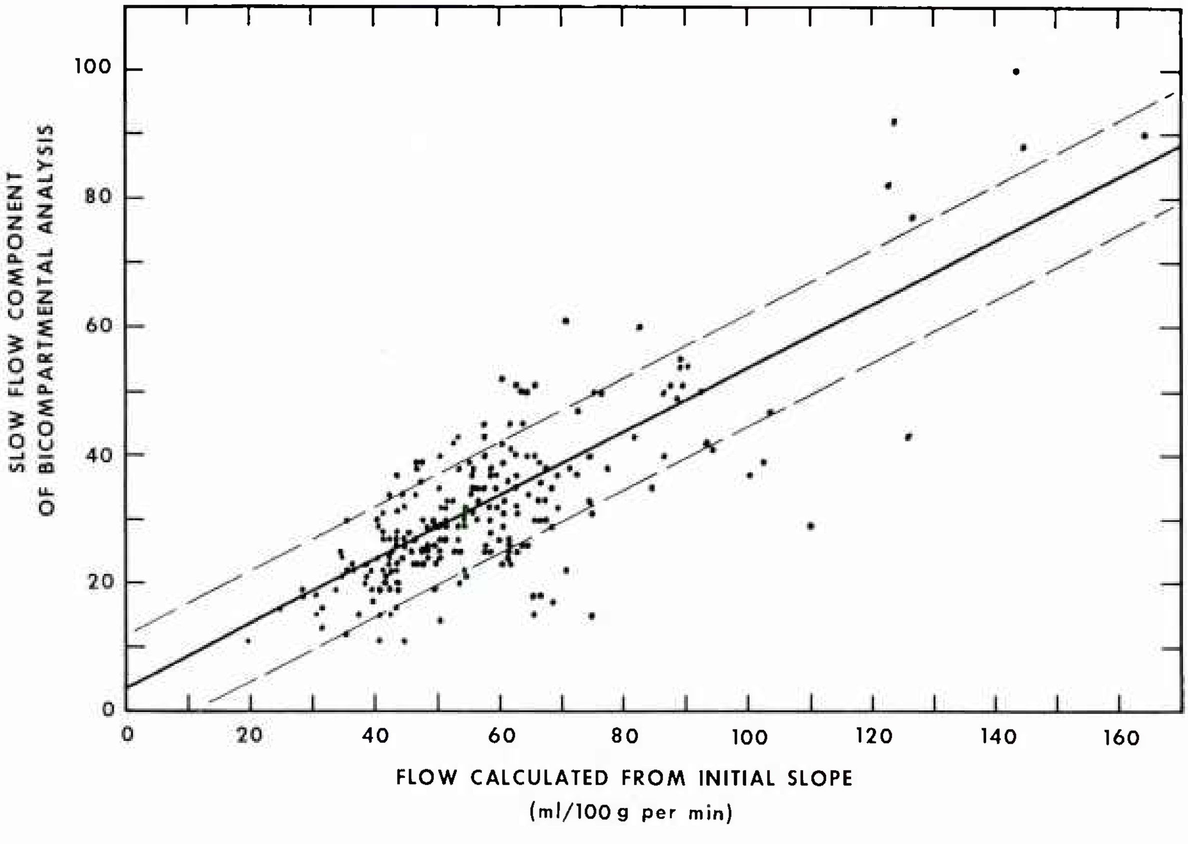

Figure 2. A linear regression analysis of the slow flow component (ordinate) and total flow calculated by initial slope index (abscissa). n = 241, correlation coefficient 0.7612 ± 8.79 S.D. about y values.

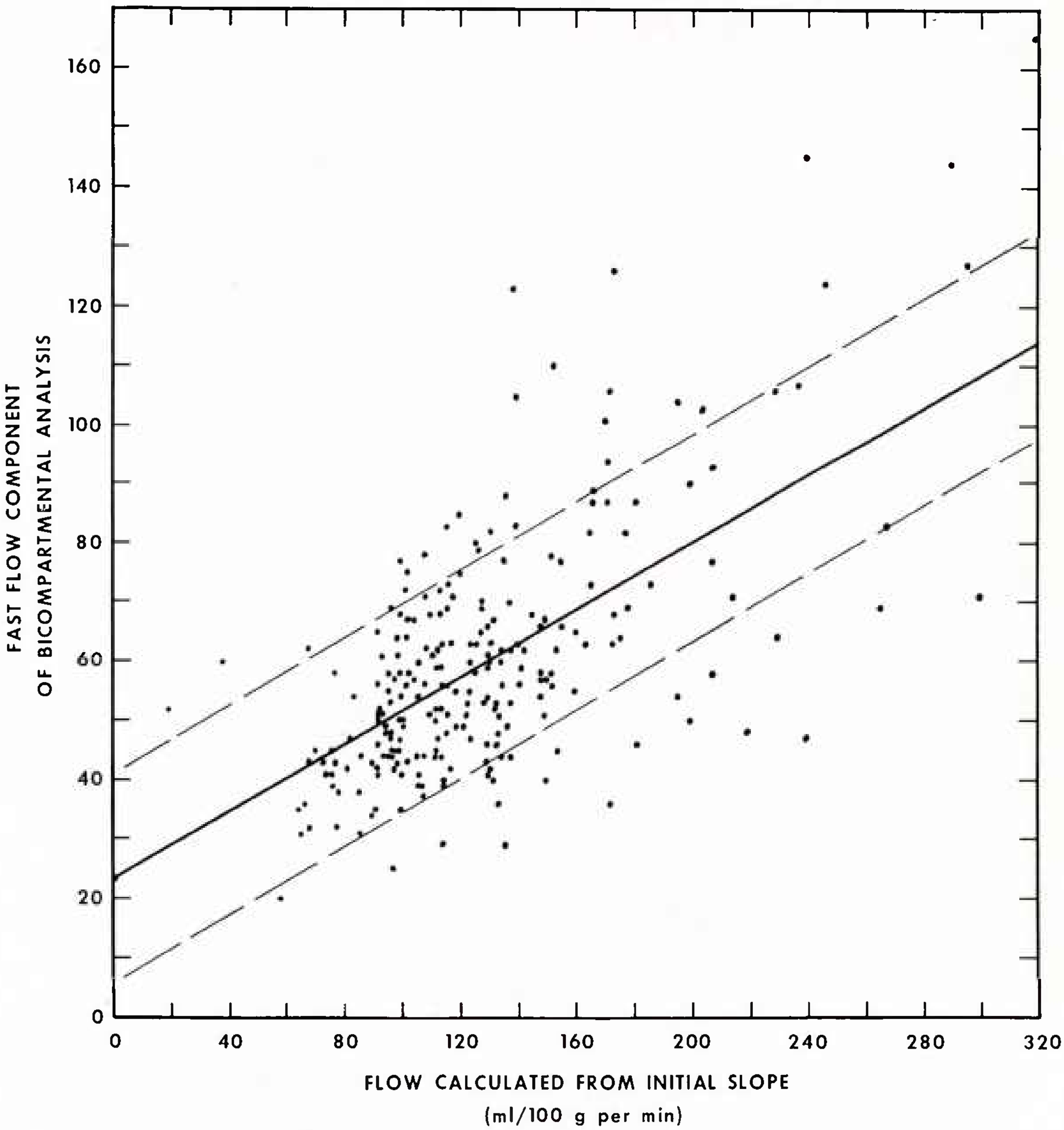

Figure 3. A linear regression analysis of the fast flow component (ordinate) and total flow calculated by initial slope index (abscissa). n = 241, correlation coefficient 0.6001 ± 17.4 S.D. about y values.

V. DISCUSSION

The initial slope index would be a correct measure of total blood flow only if the clearance curves were monoexponential, i.e., if $k_1/k_2 = 1$. If k_1 and k_2 differ by as much as 3, they can still be fitted quite well with a single exponential. Our data yield k_1/k_2 ratios ranging from 1.7 to 15 with a mean of 3.97 ± 0.15 S.D. It is surprising, therefore, how well these approximations of flow agree with the values derived from bicompartmental analyses. Flows close to 52 ml/100 g per min (the mean total cerebral blood flow value[3]) tend to be identical when measured by either method. However, low flows tend to be overestimated and high flows underestimated when calculated by the initial slope index method. A correction factor (bicompartmental value = 1.35 initial slope value -17) can easily be applied for very high and very low flow values.

VI. CONCLUSIONS

Total cerebral blood flow values measured by hydrogen clearance, when estimated from the initial 2-minute slope, agree quite well ($r = 0.928$) with those values calculated by the theoretically more correct bicompartmental analysis. This method of flow estimation has the advantage of requiring only a 2-minute steady state; and because the data dealt with are from the early part of the washout curve, minor variations of the base line have little or no effect.

REFERENCES

1. Aukland, K., Bower, B. F. and Berliner, R. W. Measurement of local blood flow with hydrogen gas. Circulation Res. 14:164-187, 1964.

2. Fieschi, C., Bozzao, L. and Agnoli, A. Regional clearance of hydrogen as a measure of cerebral blood flow. Acta Neurol. Scand. 41(Supplement 14): 46-52, 1965.

3. Martins, A. N., Kobrine, A. I., Doyle, T. F. and Ramirez, A. Total cerebral blood flow in the monkey measured by hydrogen clearance. Stroke 5:512-517, 1974.

4. Pasztor, E., Symon, L., Dorsch, N. W. C. and Branston, N. M. The hydrogen clearance method in assessment of blood flow in cortex, white matter and deep nuclei of baboons. Stroke 4:556-567, 1973.

5. Sveinsdottir, E., Thorlöf, P., Risberg, J., Ingvar, D. H. and Lassen, N. A. Calculation of regional cerebral blood flow (rCBF): initial-slope-index compared to height-over-total-area values. In: Brain and Blood Flow, Proceedings of the Fourth International Symposium on the Regulation of Cerebral Blood Flow, London, September 1970, Ross Russell, R. W., editor, pp. 85-93. London, Pitman Medical and Scientific Publishing Company Ltd, 1971.

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13. ABSTRACT

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